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1st Edition

Ontario Guidelines for the Pharmacotherapeutic Management of Diabetes Mellitus



Ontario Program for Optimal Therapeutics

Guide to the Guideline

Approach to Pharmacotherapeutic Management of Diabetes

Components of the Pharmacotherapeutic Plan

Type 1 Diabetes Mellitus

Type 2 Diabetes Mellitus

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(d) Coronary Artery Disease

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Gestational Diabetes

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Ontario Guidelines for the Pharmacotherapeutic Management of Diabetes Mellitus

Ontario Program for Optimal Therapeutics

June, 2000

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Inclusion of a pharmaceutical product in these guidelines was determined solely on the basis of the Review Panel's expert professional assessment of the available evidence. It is not intended, and cannot be taken, as a recommendation that the product be included in the reimbursement policies of any drug plan or benefits manager.

Stakeholder groups were invited to participate in the development of these guidelines by reviewing and commenting upon the guidelines in draft form. These included health care professionals, professional societies, the pharmaceutical industry and the Ontario Ministry of Health and Long-Term Care.

Comments: A form is provided at the end of the document for the submission of reader's suggestions.

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Preamble

Ontario Program for Optimal Therapeutics

SECTION 1: Guideline Preamble

Purpose of the Guidelines

These practice guidelines are designed for use by health care practitioners in the primary care setting. The intent of these guidelines is to assist the family practice physician in selecting the most appropriate medication regimen for their patients based on the best available evidence. They focus specifically on drug therapy and are intended to complement the recently published Canadian clinical practice diabetes guidelines¹ which provide recommendations for the overall management of diabetes.

Guideline development process

The guideline development process combines critical assessment of available research evidence with expert clinical opinion of clinicians and researchers. The process is overseen by a Review Panel consisting of family physicians, relevant specialists, clinical pharmacologists, pharmacists and epidemiologists representing various regions of the province, academic and community-based clinical practice, and research. The process progresses through the following stages:

- Compilation, rigorous review and critical appraisal of evidence sources, including a thorough literature search for relevant trials, meta-analyses, practice guidelines and economic analyses.
- Preparation of a draft of the guidelines, including a grade assigned to each recommendation indicating the strength of its supporting evidence, with drugs designated "first-line" or other based on the strength of efficacy data, adverse effect profile, cost, availability, convenience and other factors.
- Review and comment by a broad spectrum of external stakeholders, including all relevant health care professionals, professional societies, pharmaceutical companies, the Ministry of Health and Long-Term Care, and consumers.
- Progressive refinement of the guidelines, and formulation in final form for publication, by the Review Panel, based on their assessment of the evidence and input from the stakeholder review.

Further details of the process used to develop this consensus guideline can be obtained by contacting OPOT at the following address:

Ontario Program for Optimal Therapeutics
708-25 Charlton Ave E
Hamilton, ON, L8N 1Y2

How to Use the Guidelines

This document is divided into 5 sections. Section 1 provides background information on diabetes mellitus. Sections 2-5 provide recommendations on managing different types of patients with diabetes including the appropriate methods for preventing diabetic complications.

To find the recommended treatment for your patient:

- 1) Refer to Figure 1 on page 5 to locate the pages in Sections 2-5 that apply to your patient.
- 2) Turn to the appropriate pages in Section 2 and select the therapy most suitable for your patient from the recommended treatment options.

Grading of Recommendations

The following scheme has been used to grade the strength of the recommendations made within the practice guidelines:

GRADE A: Strong recommendation. The recommendation is based primarily upon well designed randomized controlled trials (RCT's) or meta-analyses that use clinically important outcomes.

GRADE B: Moderate recommendation. The recommendation is a combination of high quality evidence and expert opinion.

GRADE C: Weak recommendation. The recommendation is based principally upon expert opinion.

Cost of Treatments

In Section 2 the cost of each treatment is reported as an average monthly cost. The cost was calculated using the 'best available price' listed in the Ontario Drug Benefit Formulary or supplied by the manufacturer. A pharmacist's professional fee was not included in the cost of prescription items (Typical fees range from \$2 to \$12).

Figure 1: Chart for locating specific treatment recommendations

Approach to Pharmacotherapeutic Management of Diabetes		
Components of the Pharmacotherapeutic Plan	Type 1 Diabetes Mellitus	Type 2 Diabetes Mellitus
Treatment goals for glycemic control	Page 15	Page 22
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(d) Coronary Artery Disease	Page 41	Page 41
Gestational Diabetes	Page 45	

Guideline Preamble

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The views expressed in this document may not be representative of the views held by some of the individual participants, nor the institutions or organizations that they are affiliated with.

Section I

Introduction

Ontario Program for Optimal Therapeutics



Definition of Diabetes Mellitus

Diabetes is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, insulin action or both. Diabetes is associated with long-term damage, dysfunction and failure of various organs, especially eyes, kidneys, nerves, heart and blood vessels^{1,2}.

Classification of Diabetes Mellitus

Based on the Canadian Diabetes Association and American Diabetes Association approved classification system, diabetes mellitus can be divided into 4 subtypes: (a) type 1 diabetes, (b) type 2 diabetes, (c) gestational diabetes mellitus, and (d) other specific types. The last category consists of a large list of less common conditions^{1,2}.

Intermediate stages have been established to capture individuals whose glucose metabolism is not sufficiently impaired to be defined as diabetes. These individuals can have "impaired glucose tolerance" (IGT) (i.e. the fasting plasma glucose is < 7.0 mmol/L or the plasma glucose 2 hours after a 75 g glucose load is 7.8-11.0 mmol/L) or "impaired fasting glucose" (IFG) (i.e. the fasting glucose is 6.1 to 6.9 mmol/L). Although these are not identical or equivalent conditions, individuals with IGT or IFG may have a higher risk of cardiovascular disease and should undergo risk modification. Individuals with IGT or IFG generally should not be treated with medications for glycemic control but should be reassessed for diabetes yearly.

Impact of Diabetes Mellitus on Society

Diabetes Mellitus is a major health concern, personally affecting up to 10% of Canadians². It remains the leading cause of new-onset blindness and renal dysfunction. Diabetes is a principle risk factor for coronary artery disease and one of the most common complications in pregnancy. Since the discovery of insulin in 1921 by Banting, Best, McLeod and Collip numerous treatment measures have been introduced to help improve blood glucose control and prevent the long-term complications of diabetes.

Table 1: Prevalence of diabetes (diagnosed and undiagnosed) based on NHANES III³

Age (years)	Prevalence
<20	0.3%
20-39	1.6%
40-74	12.3%
>74	19.3%

NOTE:

* based on the American Diabetes Association's definition of diabetes: FPG $\geq$ 7mmol/L

Goals of Therapy

The goals in managing diabetes are 3 fold:

1. to avoid the acute complications (e.g. ketoacidosis, hyperglycemia, infection),
2. to prevent long-term complications
 - a) microvascular complications: nephropathy, retinopathy, neuropathy
 - b) macrovascular complications: coronary artery disease, atherosclerosis, peripheral vascular disease
3. to minimize negative sequelae associated with therapies (eg. hypoglycemia, weight gain).

Any decrease in elevated blood glucose will result in a decrease in the overall risk of complications regardless of the initial blood glucose concentrations.

Example

In a patient with type 2 diabetes, every 1% decrease in HbA _{1c} (regardless of baseline value) results in...
--

...a 25% reduction in diabetes-related death
--

...a 7% reduction in all-cause mortality, and

...an 18% reduction in combined fatal and nonfatal myocardial infarction ⁴ .

Section II

Type 1 Diabetes

Ontario Program for Optimal Therapeutics

**IMPORTANT NOTE CONCERNING THE FOLLOWING
PAGES**

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TWICE IN ORDER TO OBTAIN THE BEST
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Section II: Type 1 Diabetes

Type 1 diabetes is characterized by beta-cell destruction within the pancreas leading to absolute insulin deficiency and dependence on exogenous insulin administration to prevent ketoacidosis^{1,2}.

Guiding Principles:

Approach to Management

1. The administration of insulin is essential in type 1 diabetes to maintain glycemic control and prevent acute complications. There is no known effective primary prevention strategy for type 1 diabetes.
2. All patients should be managed through three important means:
 - (a) education – education is an important component of diabetes management
 - (b) nutrition (diet), and
 - (c) insulin therapy.
3. Insulin therapy should be adjusted to provide the best degree of glycemic control possible as there is no glycemic threshold for reducing the risk of microvascular complications³.
4. Intensive insulin therapy reduces long-term microvascular complications including nephropathy^{7,8}, retinopathy^{7,8} and neuropathy⁹ but there may be an increase in hypoglycemia associated with intensive therapy⁹. (The principles of intensive insulin therapy are described on page 14.)
5. The selection of a regimen should be based on:
 - (a) compatibility with the patient's daily schedule
 - (b) the patient's response to past insulin regimens
 - (c) factors in the patient's lifestyle which may influence glycemic control (eg. eating patterns, exercise etc).
6. Oral hypoglycemics are not appropriate for the management of type 1 diabetes.

Children and Adolescents

1. The majority of children and adolescents with diabetes have type 1 diabetes.
2. Children and adolescents with new onset type 1 diabetes should be started on insulin therapy within 24 hours.
3. Children and adolescents with type 1 diabetes should be referred to a diabetes specialist at the time of onset and should subsequently receive shared care from the primary care physician and the specialist.
4. Extreme caution is required to avoid hypoglycemia in children under 5 years of age, because of the permanent cognitive deficit that may occur in this age group¹⁰.
5. Initial outpatient management and education should be considered for all children and adolescents with new-onset diabetes if appropriate personnel and a 24-hour telephone consultation service are available in the community¹¹. Inpatient management is no longer necessary for initial management if these resources are available. **However, the presence of ketoacidosis requires hospitalization.**



Section II: Type 1 Diabetes

Type 1 diabetes is characterized by beta-cell destruction within the pancreas leading to absolute insulin deficiency and dependence on exogenous insulin administration to prevent ketoacidosis¹².

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Approach to Management

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4. Intensive insulin therapy reduces long-term microvascular complications including nephropathy^{7a}, retinopathy^{7a} and neuropathy⁸ but there may be an increase in hypoglycemia associated with intensive therapy⁹. (The principles of intensive insulin therapy are described on page 14.)
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Intensive Insulin Therapy

- Optimal diabetes therapy requires multiple daily injections (or continuous insulin infusion insulin pump) combined with regular blood glucose monitoring (4 or more times daily), and adjusting of therapy by the patient to achieve optimal levels of glycemic control.
- Insulin therapy is generally administered by syringe, pen injector, or insulin pump. Insulin pumps provide a continuous subcutaneous insulin infusion (CSII). The use of an insulin pump necessitates the same discipline as with multiple injections. The cost of this device may be prohibitive for individuals not covered by a drug plan that will pay for these devices.
- All currently marketed glucose monitoring devices, when used correctly, provide similar quality of results. The cost of glucose monitoring devices and strips vary depending upon the additional features of the apparatus. The choice of monitoring device may be subject to the patient's dexterity, vision, lifestyle and economic factors.

Management of Type 1 Diabetes

Establish treatment goals for glycemic control

Table 2: Treatment goals for glycemic control¹

Parameters	Normal Non-Diabetic	Optimal Glycemic Control*	Suboptimal Glycemic Control [†]	Inadequate Glycemic Control
Target HbA _{1c} (%)				
Ages > 12 y.o. [‡]	4.0 to 6.0	< 7.0	7.0 - 8.4	> 8.4
Ages 5 to 12 y.o. [§]	4.0 to 6.0	≤ 8.4	> 8.4	undefined
Ages < 5 y.o. [§]	4.0 to 6.0	individualized [¶]	undefined	undefined
Target fasting or preprandial blood glucose (mmol/L)				
Ages > 12 y.o. [‡]	3.8 to 6.1	4.0 to 7.0	7.1 to 10.0	> 10.0
Ages 5 to 12 y.o. [§]	undefined	4.0 to 10.0	> 10.0	undefined
Ages < 5 y.o. [§]	undefined	6.0 to 12.0	> 12.0	undefined
Target 1 to 2 hours postprandial blood glucose (mmol/L)				
Ages > 12 y.o. [‡]	4.4 to 7.0	5.0 to 11.0	11.1 to 14.0	> 14.0
Ages ≤ 12 y.o. [§]	undefined	undefined	undefined	undefined

NOTE:

- * The goals established for optimal glycemic control reflects target ranges established in 2 landmark trials: the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study.
- † Target ranges specified for optimal glycemic control should serve as a goal for most patients. Certain patients may be less suited for achieving these target ranges in which case suboptimal glycemic control ranges may be used. (Refer to the table on page 16 for suitability criteria of patients with type 1 diabetes).
- ‡ The same glucose targets apply to otherwise healthy elderly as to younger people with diabetes¹. Target values and treatment approaches for adolescents 12 and older are the same as those for adults⁵. Patients with multiple comorbidity may necessitate treatment goals to be adjusted based on individual needs to avoid symptoms of hyperglycemia and prevent hypoglycemia¹.
- § Treatment goals for patients < 12 years of age were established by the consensus panel with reference to the Canadian guidelines¹. Children and adolescents with type 1 diabetes should be referred to a diabetes specialist and should receive shared care from the primary care physician and the diabetes specialist thereafter.
- || Corresponds to 140% of the upper limit of normal non-diabetics¹.
- ¶ Treatment goals should be individualized in consultation with a specialist.

Management of Type 1 Diabetes

Establish treatment goals for glycemic control

Table 2: Treatment goals for glycemic control[†]

Parameters	Normal Non-Diabetic	Optimal Glycemic Control*	Suboptimal Glycemic Control [†]	Inadequate Glycemic Control
Target HbA _{1c} (%) Ages > 12 y.o. [‡] Ages 5 to 12 y.o. [§] Ages < 5 y.o. [¶]	4.0 to 6.0 4.0 to 6.0 4.0 to 6.0	< 7.0 ≤ 8.4 individualized ^{¶¶}	7.0 - 8.4 > 8.4 undefined	> 8.4 undefined undefined
Target fasting or preprandial blood glucose (mmol/L) Ages > 12 y.o. [‡] Ages 5 to 12 y.o. [§] Ages < 5 y.o. [¶]	3.8 to 6.1 undefined undefined	4.0 to 7.0 4.0 to 10.0 6.0 to 12.0	7.1 to 10.0 > 10.0 > 12.0	> 10.0 undefined undefined
Target 1 to 2 hours postprandial blood glucose (mmol/L) Ages > 12 y.o. [‡] Ages ≤ 12 y.o. [§]	4.4 to 7.0 undefined	5.0 to 11.0 undefined	11.1 to 14.0 undefined	> 14.0 undefined

NOTE:

* The goals established for optimal glycemic control reflects target ranges established in 2 landmark trials: the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study.

† Target ranges specified for optimal glycemic control should serve as a goal for most patients. Certain patients may be less suited for achieving these target ranges in which case suboptimal glycemic control ranges may be used. (Refer to the table on page 16 for suitability criteria of patients with type 1 diabetes).

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|| Corresponds to 140% of the upper limit of normal non-diabetics¹.

¶¶ Treatment goals should be individualized in consultation with a specialist.

Section II: Type 1 Diabetes

Patient characteristics and contraindications for intensive insulin therapy are outlined below in Table 3.

To achieve optimal glycemia all patients should be encouraged to adopt intensive insulin therapy, except for patients with relative and absolute contraindications.

Table 3: Factors affecting suitability for intensive insulin therapy

Ideal characteristics	Relative contraindications	Absolute contraindications
(a) Highly motivated (b) Willing to monitor blood glucose 4 or more times daily (c) Willing to inject insulin 3 or more times daily OR willing to maintain an insulin pump (d) Able to access diabetes support services	(a) Children aged 5 to 12 years old (since hypoglycemic episodes can impair the development of the brain which does not fully develop until the age of 12) (b) End-stage renal disease	(a) Children < 5 years old (b) Individuals unwilling or unable to actively participate in their glucose management (e.g. visual impairment) (c) Patients with dementia or cognitive impairment and in the absence of sufficient caregiver support

NOTE:

In patients with a history of hypoglycemic unawareness or a history of severe hypoglycemic episode intensive insulin therapy can be used; however, glycemic targets have to be appropriately increased to prevent hypoglycemia (i.e. fasting and pre-meal plasma glucose goal of 6-10 mmol/L).

Section II: Type 1 Diabetes

Patient characteristics and contraindications for intensive insulin therapy are outlined below in Table 3.

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Table 3: Factors affecting suitability for intensive insulin therapy¹²

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In patients with a history of hypoglycemic unawareness or a history of severe hypoglycemic episode intensive insulin therapy can be used; however, glycemic targets have to be appropriately increased to prevent hypoglycemia (i.e. fasting and pre-meal plasma glucose goal of 6-10 mmol/L).

Institute non-pharmacologic measures for glycemic control

Recommendations:

- ◆ Education and nutrition (diet) therapy, **always in combination with insulin therapy**, are recommended as a first line approach to improve glycemic control¹³⁻¹⁵.
- ◆ Referral to a diabetes educator and/or dietician is recommended when possible. Ideally this should occur around the time of diagnosis and periodically thereafter.

Grade of recommendations - B

NOTE:

Refer to the Canadian clinical practice diabetes guidelines for additional recommendations for instituting non-pharmacologic measures¹.



Institute pharmacologic measures for glycemic control

Recommendations:

- ♦ Optimal glycemic control requires multiple insulin injections to mimic both basal insulin secretion and mealtime insulin surges. A combination of insulin products can be used to achieve the desired glycemic control.
- ♦ Basal insulin secretion may be mimicked using intermediate or long-acting insulin.
- ♦ Mealtime insulin surges can be reproduced using short-acting insulin/insulin analogue or a combination of intermediate insulin and short-acting insulin/insulin analogue.

Grade of recommendations – A

Recommendations:

- ♦ A short-acting insulin analogue (lispro) may be of particular benefit for patients with:
 - (a) a history of severe hypoglycemia¹⁶
 - (b) unpredictable eating times
 - (c) children who won't take interprandial snacks
 - (d) continuous subcutaneous insulin infusions (CSII) or pumps
- ♦ In other circumstances regular insulin or a short-acting insulin analogue (lispro) may be used. Regular insulin may be considered first line therapy based on its comparable effects on HbA_{1c} and lower cost¹⁷. Lispro, however, may be used preferentially based on growing evidence supporting its superiority with respect to ease of use, impact on quality of life, and lower risk of hypoglycemia with intensive therapy¹⁸⁻²⁰.

Grade of recommendations – B

Table 4: Insulin preparations available in Canada

<i>Insulin Preparations</i>	<i>Approximate Cost Per 1000 Units (\$)</i>
Short-acting insulin/insulin analogue	
lispro	23.00
regular	16.00
insulin aspart*	Not available
Intermediate-acting insulin	
insulin isophane (NPH)	16.00
insulin zinc (lente)	16.00
Long-acting insulin	
insulin zinc (ultralente), extended	16.00 16.00

NOTE:

* Insulin aspart is a short-acting insulin analogue not yet available in Canada.

Premixed combinations of short and intermediate-acting insulins are generally not appropriate for patients with type 1 diabetes.

Insulin zinc (lente or ultralente) must not be mixed and left to stand (> 5 minutes) with short-acting insulin as excess zinc in insulin zinc will bind with regular insulin and slow its onset of action.

Institute pharmacologic measures for glycemic control

Recommendations:

- ◆ Optimal glycemic control requires multiple insulin injections to mimic both basal insulin secretion and mealtime insulin surges. A combination of insulin products can be used to achieve the desired glycemic control.
- ◆ Basal insulin secretion may be mimicked using intermediate or long-acting insulin.
- ◆ Mealtime insulin surges can be reproduced using short-acting insulin/insulin analogue or a combination of intermediate insulin and short-acting insulin/insulin analogue.

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insulin zinc (lente)	16.00
Long-acting insulin	
insulin zinc (ultralente), extended	16.00 16.00

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Section III

Type 2 Diabetes

Ontario Program for Optimal Therapeutics

Type 2 diabetes is the most common type of diabetes, characterized by impaired glucose metabolism ranging from predominant insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance². Patients with type 2 diabetes most often present as asymptomatic or mildly symptomatic and rarely with ketoacidosis.

Guiding Principles:

1. Type 2 diabetes is a progressive disease with modifiable risk factors. Treatment can be expected to escalate with time. More than 50% of patients managed with non-pharmacologic measures will become symptomatic and will require drug therapy after 1 year²¹. Approximately 50% of patients with type 2 diabetes managed on monotherapy require additional therapy at 3 years in order to maintain optimal glycemic control.
2. 80-90% of patients with type 2 diabetes are overweight. Measures to reduce weight may improve glycemic control in these patients.
3. The prevention and management of microvascular complications (i.e. retinopathy, nephropathy and neuropathy) represent a principal component of diabetes care. More than one third of patients with newly diagnosed type 2 diabetes present with microvascular complications²².
4. Type 2 diabetes increases the risk of coronary artery disease by at least 200% in men and up to 500% in women. Optimizing lipid levels, anti-platelet therapy and ACE inhibitor therapy also help to reduce this risk.
5. The goals in managing type 2 diabetes include:
 - (a) preventing symptoms of hyperglycemia including fatigue, nocturia, etc.
 - (b) preventing macrovascular and microvascular complications
 - (c) improving quality of life.

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Guiding Principles:

1. Type 2 diabetes is a progressive disease with modifiable risk factors. Treatment can be expected to escalate with time. More than 50% of patients managed with non-pharmacologic measures will become symptomatic and will require drug therapy after 1 year²¹. Approximately 50% of patients with type 2 diabetes managed on monotherapy require additional therapy at 3 years in order to maintain optimal glycemic control.
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 - (a) preventing symptoms of hyperglycemia including fatigue, nocturia, etc.
 - (b) preventing macrovascular and microvascular complications
 - (c) improving quality of life.

Establish treatment goals for glycemic control

Table 5: Treatment goals for glycemic control¹

Parameters	Normal Non-Diabetic	Optimal Glycemic Control*	Suboptimal Glycemic Control [†]	Inadequate Glycemic Control
Target HbA _{1c} (%)	4.0 - 6.0	< 7.0	7.0 - 8.4	> 8.4
Target fasting or preprandial blood glucose (mmol/L)	3.8 - 6.1	4.0 - 7.0	7.1 - 10.0	> 10.0
Target 1-2 hours postprandial blood glucose (mmol/L)	4.4 - 7.0	5.0-11.0	11.1-14.0	>14.0

NOTE:

The same glucose targets apply to otherwise healthy elderly as to younger people with diabetes¹.

Patients with multiple comorbidity may necessitate treatment goals to be adjusted based on individual needs to avoid symptoms of hyperglycemia and prevent hypoglycemia¹.

* The goals established for optimal glycemic control reflects target ranges established in 2 landmark trials: the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study.

† Target ranges specified for optimal glycemic control should serve as a goal for most patients. Certain patients may be less suited for these target ranges in which case suboptimal glycemic control ranges may be used.

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NOTE:

The same glucose targets apply to otherwise healthy elderly as to younger people with diabetes¹. Patients with multiple comorbidity may necessitate treatment goals to be adjusted based on individual needs to avoid symptoms of hyperglycemia and prevent hypoglycemia¹.

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† Target ranges specified for optimal glycemic control should serve as a goal for most patients. Certain patients may be less suited for these target ranges in which case suboptimal glycemic control ranges may be used.

Institute non-pharmacologic measures for glycemic control

Recommendations:

- ◆ Nutrition (diet) therapy in combination with physical activities are recommended as the first line approach to improve glycemic control^{14,15}.
- ◆ Patients should be referred to a diabetes educator and/or dietician when possible.
- ◆ These measures are also recommended as a first line approach to weight loss in obese patients ($\text{BMI} \geq 30 \text{ kg/m}^2$)^{23,24}.

Grade of recommendations - B

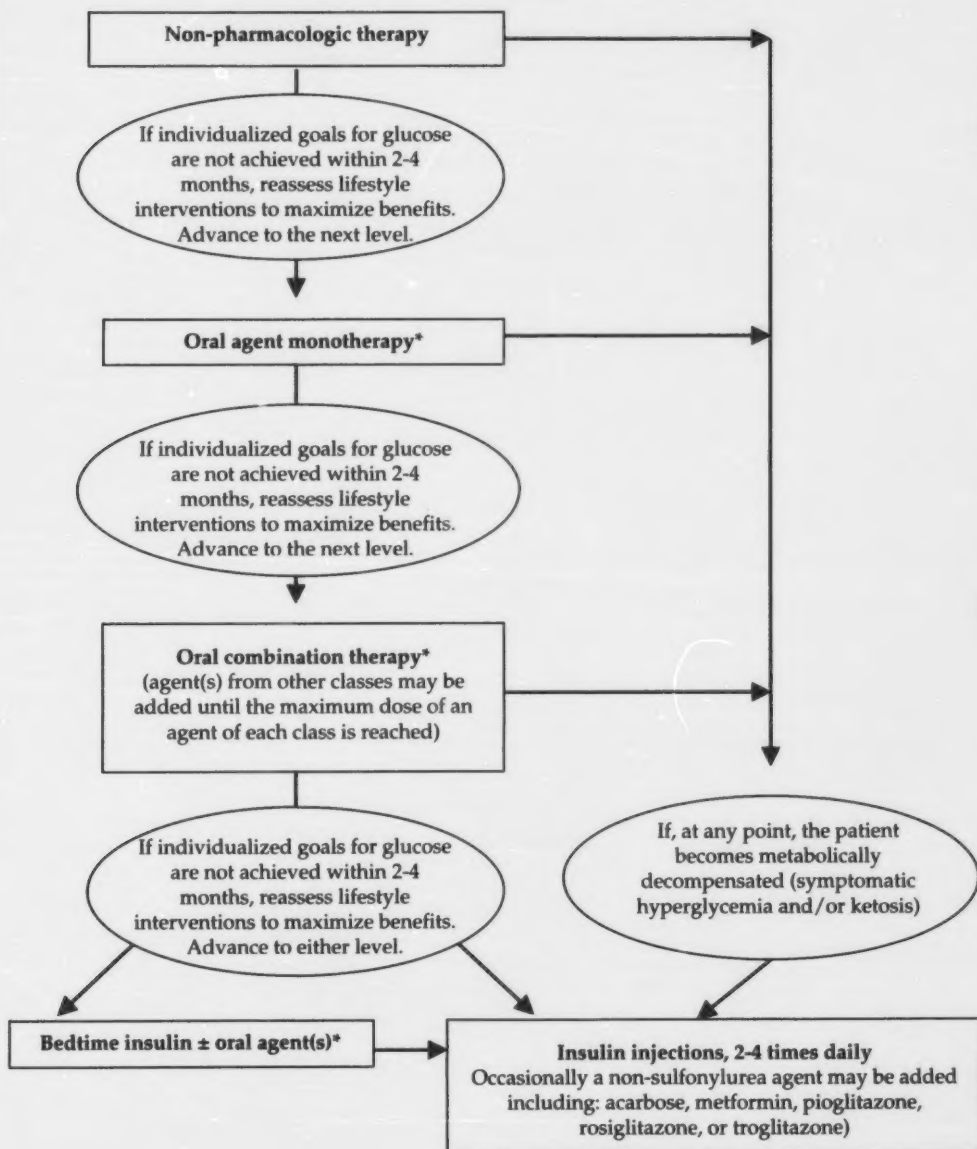
NOTE:

More than 50% of patients managed through non-pharmacologic measures will become symptomatic and will require drug therapy after 1 year²¹.

* BMI = body mass index (Refer to page 62 for a nomogram to calculate BMI)

Institute pharmacologic measures for glycemic control

Figure 2: Algorithm for adding drug therapy¹



NOTE:

* Oral agents include: acarbose, gliclazide, glyburide, metformin, pioglitazone, repaglinide, rosiglitazone, or troglitazone.

Metformin, gliclazide and glyburide are recommended as first line agents based on the availability of well-designed clinical trials demonstrating a reduction in diabetic complications with biguanides and sulfonylureas.

Oral agents – Monotherapy or combination therapy

Recommendations:

- ◆ In obese patients ($\text{BMI} \geq 30 \text{ kg/m}^2$)*, if non-pharmacologic measures are inadequate, metformin is recommended as the first line drug therapy^{25,26}.
- ◆ Metformin should not be used in patients at increased risk of lactic acidosis, including those with impaired renal function†, hepatic disease, alcoholism, symptomatic congestive heart failure and those undergoing any intravascular radiocontrast study²⁷.
- ◆ In obese patients ($\text{BMI} \geq 30 \text{ g/m}^2$)*, sulfonylureas should be reserved as second line therapy unless metformin is contraindicated or not tolerated^{26,28}.
- ◆ Non-obese patients should be initiated on a sulfonylurea or metformin^{25,28}.
- ◆ Sulfonylureas may be added to metformin to improve glycemic control^{26,29,30}.
- ◆ To improve glycemic control, acarbose or a thiazolidinedione (glitazone) may be added to diet, sulfonylurea, or metformin therapy^{31,32}. Repaglinide may be added to diet or metformin therapy.

Grade of recommendations - A

NOTE:

- * BMI = body mass index (Refer to page 62 for a nomogram to calculate BMI)
- † Serum creatinine $\geq 136 \text{ umol/L}$ in males, serum creatinine $\geq 124 \text{ umol/L}$ in females or abnormal creatinine clearance
- ‡ Metformin may be initiated when creatinine levels return to normal after contrasting procedures.
- § In one study when metformin was added to sulfonylurea therapy there was an increased risk of diabetes-related death²⁶. The clinical importance of this finding is not yet certain.

Table 6: Biguanides available in Canada

<i>Name</i>	<i>Recommended Daily Dosage</i>	<i>Daily Cost (\$)</i>
metformin	500-1000 mg twice daily	0.24-0.49



Section III: Type 2 Diabetes

Oral agents – Monotherapy or combination therapy

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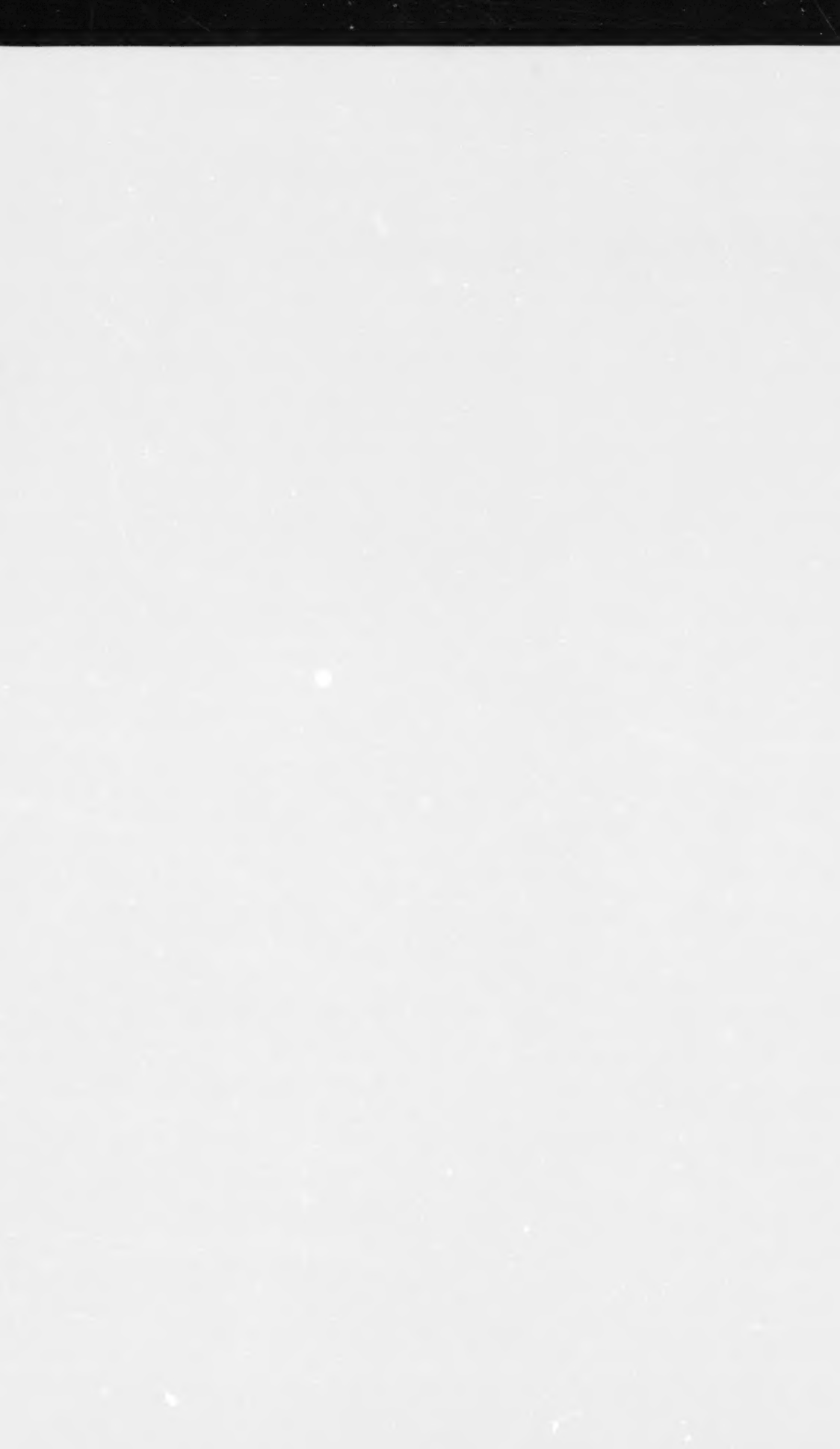
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Section III: Type 2 Diabetes

Table 7: Sulfonylureas available in Canada

<i>Name</i>	<i>Recommended Daily Dosage</i>	<i>Daily Cost (\$)</i>
gliclazide	40-160 mg 2 times daily	0.37-1.49
or		
glyburide	1.25-10 mg 1-2 times daily	0.02-0.27

NOTE:

Gliclazide may be associated with a lower frequency of hypoglycemia¹¹.

Chlorpropamide and acetohexamide are not listed due to excessive risk of hypoglycemia attributed to prolonged activity secondary to a long half-life or accumulation of active metabolites.

Chlorpropamide is also associated with an increased risk of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and disulfiram-like reactions. Although these agents are not recommended, they do not need to be discontinued in patients that are already on one of them and are achieving the desired effects.

Tolbutamide is not listed on the basis of its less convenient dosing schedule and its possible association with increased mortality¹².

Table 8: Alpha-Glucosidase Inhibitors available in Canada

<i>Name</i>	<i>Recommended daily dose</i>	<i>Daily Cost (\$)</i>
acarbose	25-100 mg tid	0.34-0.94

Table 9: Thiazolidinediones

<i>Name</i>	<i>Recommended Daily Dose</i>	<i>Daily Cost (\$)</i>
pioglitazone	15-45 mg once daily	2.46-4.15
or		
rosiglitazone	4-8 mg once daily	2.46-2.75
or		
troglitazone	200-600 mg once daily	Not available

Table 10: Meglitinides available in Canada

<i>Name</i>	<i>Recommended Daily Dose</i>	<i>Daily Cost (\$)</i>
repaglinide	0.5-4 mg 2-4 times daily ac	0.50-2.16

Section III: Type 2 Diabetes

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Insulin – single or multiple injections

Recommendations:

- ◆ If an adequate trial of lifestyle changes and oral agents is unsuccessful (2-4 months trial period), insulin therapy should be initiated^{25,35}.
- ◆ If oral hypoglycemics fail, an evening dose of basal insulin in addition to 1 or 2 oral agents is recommended before initiating multiple insulin injections^{30,36}.
- ◆ Conversion to multiple daily insulin may reduce cardiovascular complications in patients with type 2 diabetes following an acute myocardial infarction³⁷.
- ◆ Poor glucose control despite insulin therapy can be improved by the addition of metformin^{38,39}, acarbose⁴⁰, or a thiazolidinedione (glitazone)⁴⁰.

Grade of recommendations - A

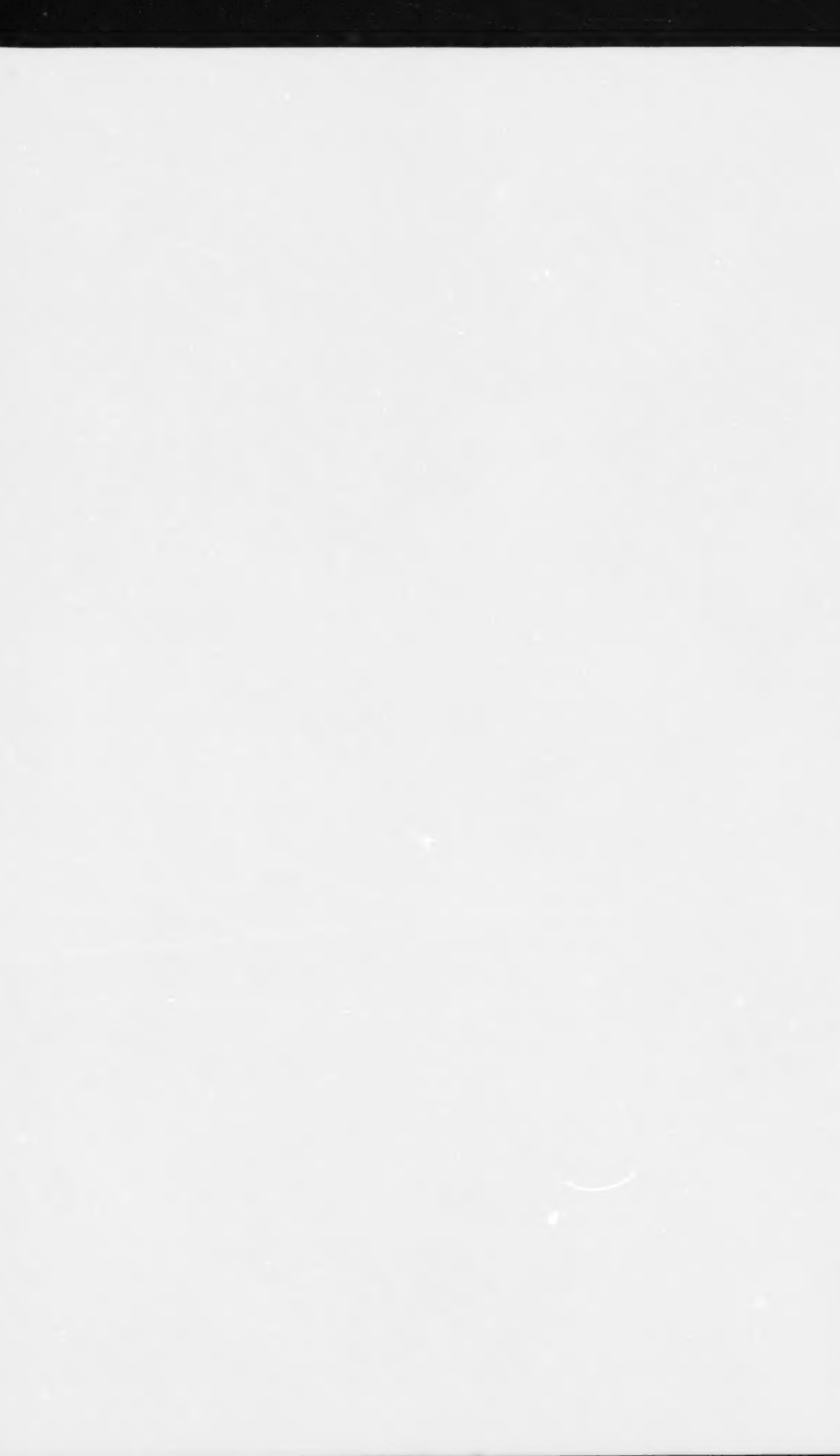
NOTE:

High doses of insulin are often required to achieve optimal glycemic control.

Recommendations:

- ◆ Short-acting insulin analogues (lispro) may be of particular benefit for patients with:
 - (a) a history of severe hypoglycemia¹⁶
 - (b) unpredictable eating times
- ◆ In other circumstances regular insulin or a short-acting insulin analogue (lispro) may be used. Regular insulin may be considered first line therapy based on its comparable effects on HbA_{1c} and lower cost¹⁷. Lispro, however, may be used preferentially based on growing evidence supporting its superiority with respect to ease of use and impact on quality of life¹⁸⁻²⁰.

Grade of recommendations - B



Section III: Type 2 Diabetes

Table 11: Insulin preparations available in Canada

<i>Insulin Preparations</i>	<i>Approximate Cost Per 1000 Units (\$)</i>
<i>Short-acting insulin/insulin analogue</i>	
lispro	23.00
regular	16.00
insulin aspart*	Not available
<i>Intermediate-acting insulin</i>	
insulin isophane (NPH)	16.00
insulin zinc (lente)	16.00
<i>Long-acting insulin</i>	
insulin zinc (ultralente), extended	16.00 16.00

NOTE:

Pre-mixed combinations of insulin isophane (NPH) and regular are also available in the following proportions: 10/90, 20/80, 30/70, 40/60, 50/50.

A pre-mixed combination of lispro and insulin isophane (NPL) is available in the following proportion: 25/75.

Insulin zinc (lente or ultralente) must not be mixed with regular insulin and left to stand (> 5 minutes) as excess zinc in insulin zinc will bind with regular insulin and slow its onset of action. Premixed insulin should be reserved for convenience and in patients with reduced ability to avoid dosing errors and hypoglycemia.

* Insulin aspart is a short-acting insulin analogue not yet available in Canada.

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* Insulin aspart is a short-acting insulin analogue not yet available in Canada.

Section IV

Preventing Complications



(a) Nephropathy

Type 1 Diabetes

Recommendations:

- ◆ ACE inhibitors are recommended for all postpubertal patients with type 1 diabetes with either persistent microalbuminuria⁴¹⁻⁴⁵, or macroalbuminuria^{46,47}, (including normotensive patients), to slow the progression of nephropathy.

Grade of recommendations – A**NOTE:**

Microalbuminuria is defined as excreting albumin between 30-300 mg/24 hours or 20-200 ug/min of albumin.

Macroalbuminuria is defined as excreting albumin >300 mg/24 hours or 200 ug/min.

Microalbuminuria can be confirmed if 2 out of 3 random daytime urine samples taken over 3 months present with an albumin:creatinine ratio greater than 2.8 for females and 2.0 for males¹.

ACE inhibitors can cause injury or death to the developing fetus when used in pregnancy during the second and third trimester⁴⁸.

Type 2 Diabetes

Recommendations:

- ◆ ACE inhibitors should be added in all patients with type 2 diabetes with either persistent microalbuminuria or macroalbuminuria (including normotensive patients)^{44,49-51}, to slow the progression of nephropathy.

Grade of recommendations – A**NOTE:**

Microalbuminuria is defined as excreting albumin between 30-300 mg/24 hours or 20-200 ug/min of albumin.

Macroalbuminuria is defined as excreting albumin >300 mg/24 hours or 200 ug/minute.

Microalbuminuria can be confirmed if 2 out of 3 random daytime urine samples taken over 3 months present with an albumin:creatinine ratio greater than 2.8 for females and 2.0 for males¹.

ACE inhibitors can cause injury or death to the developing fetus when used in pregnancy during the second and third trimester⁴⁸.

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Section IV: Preventing Complications

Table 12: ACE inhibitors available in Canada for the prevention of the progression of nephropathy

<i>Name</i>	<i>Starting Dose*</i>	<i>Optimal Dose</i>	<i>Daily Cost (\$)</i>
Agents with published randomized controlled trials supporting this indication†			
captopril	6.25 mg (test dose)	25-50 mg three times daily	0.90-1.68
or			
enalapril	2.5-5 mg once daily	10 mg once daily	0.96
or			
lisinopril	2.5-10 mg once daily	10-20 mg once daily	0.81-0.97
or			
ramipril	1.25-2.5 mg once daily	2.5-5 mg once daily	0.75
Agents without published randomized controlled trials supporting this indication			
benazepril	10 mg once daily	10-40 mg once daily	0.68-1.56
or			
cilazapril	2.5-5 mg once daily	2.5-5 mg once daily	0.68-0.79
or			
fosinopril	10 mg once daily	10-20 mg once daily	0.79-0.95
or			
perindopril	2-4 mg once daily	4-8 mg once daily	0.75-1.50
or			
quinapril	10 mg once daily	10-40 mg once daily	0.82
or			
trandolapril	0.5-1 mg once daily	0.5-4 mg once daily	0.34-1.54

NOTE:

Potassium concentrations may be evaluated periodically while on an ACE inhibitor.

* Patients on concomitant diuretic therapy should, if possible, discontinue the diuretic 2-3 days before starting the ACE inhibitor to minimize hypotension. Otherwise the lowest possible starting dose should be taken under close medical supervision.

† Published trials include patients with either type 1 or type 2 diabetes. The following doses were used in the clinical trials: captopril 25-50 mg twice daily^{11,43,45,46,52,53}; enalapril 10 mg daily^{44,54,55}; lisinopril 10-20 mg daily^{56,57}; ramipril 2.5-5 mg daily⁵⁸.

(b) Hypertension

Type 1 and Type 2 Diabetes

Recommendations:

- ◆ Patients with diabetes and elevated blood pressure ($> 140/90$ mmHg) should receive medication for the management of hypertension. The desired endpoint is a blood pressure $< 130/80$ mmHg¹.
- ◆ Often up to 3 drugs may be needed to achieve the desired blood pressure control in this patient population⁹.
- ◆ Treatment recommendations for patients with diabetes and hypertension are subdivided into the following 3 patient subgroups:
 - i) patients with overt nephropathy
 - ii) patients without overt nephropathy and < 60 years of age
 - iii) patients without overt nephropathy and ≥ 60 years of age.

Grade of recommendations – B

Recommendations:

For patients with all of the following conditions:

- diabetes mellitus
- hypertension (BP $\geq 140/90$ mmHg)
- overt nephropathy (albuminuria ≥ 300 mg/day).

First Line Therapy:

	RECOMMENDED AGENTS	PAGE LISTING SPECIFIC AGENTS	GRADE OF RECOMMENDATION
	ACE inhibitor	Page 36	A
Special Circumstances:			
<i>If ACE inhibitors are not tolerated USE</i>	angiotensin II antagonist	Page 38	B

NOTE:

Refer to other references for more details on the management of hypertension¹⁰.

- * In the UKPDS, ACE inhibitors and beta-blockers were not significantly different with respect to blood pressure control and prevention of microalbuminuria and proteinuria. Beta-blocker therapy may be less desirable based on its masking effect of adrenergic symptoms of hypoglycemia.

Section IV: Preventing Complications

Table 12: ACE inhibitors available in Canada for the prevention of the progression of nephropathy

<i>Name</i>	<i>Starting Dose*</i>	<i>Optimal Dose</i>	<i>Daily Cost (\$)</i>
Agents with published randomized controlled trials supporting this indication [†]			
captopril	6.25 mg (test dose)	25-50 mg three times daily	0.90-1.68
or			
enalapril	2.5-5 mg once daily	10 mg once daily	0.96
or			
lisinopril	2.5-10 mg once daily	10-20 mg once daily	0.81-0.97
or			
ramipril	1.25-2.5 mg once daily	2.5-5 mg once daily	0.75
Agents without published randomized controlled trials supporting this indication			
benazepril	10 mg once daily	10-40 mg once daily	0.68-1.56
or			
cilazapril	2.5-5 mg once daily	2.5-5 mg once daily	0.68-0.79
or			
fosinopril	10 mg once daily	10-20 mg once daily	0.79-0.95
or			
perindopril	2-4 mg once daily	4-8 mg once daily	0.75-1.50
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or			
trandolapril	0.5-1 mg once daily	0.5-4 mg once daily	0.34-1.54

NOTE:

Potassium concentrations may be evaluated periodically while on an ACE inhibitor.

* Patients on concomitant diuretic therapy should, if possible, discontinue the diuretic 2-3 days before starting the ACE inhibitor to minimize hypotension. Otherwise the lowest possible starting dose should be taken under close medical supervision.

† Published trials include patients with either type 1 or type 2 diabetes. The following doses were used in the clinical trials: captopril 25-50 mg twice daily^[1,10,13,16,21]; enalapril 10 mg daily^[14,15]; lisinopril 10-20 mg daily^[6,27]; ramipril 2.5-5 mg daily^[8].

(b) Hypertension

Type 1 and Type 2 Diabetes

Recommendations:

- ◆ Patients with diabetes and elevated blood pressure ($> 140/90$ mmHg) should receive medication for the management of hypertension. The desired endpoint is a blood pressure $<130/80$ mmHg[†].
- ◆ Often up to 3 drugs may be needed to achieve the desired blood pressure control in this patient population⁹⁰.
- ◆ Treatment recommendations for patients with diabetes and hypertension are subdivided into the following 3 patient subgroups:
 - i) patients with overt nephropathy
 - ii) patients without overt nephropathy and < 60 years of age
 - iii) patients without overt nephropathy and ≥ 60 years of age.

Grade of recommendations – B

Recommendations:

For patients with all of the following conditions:

- diabetes mellitus
- hypertension (BP $\geq 140/90$ mmHg)
- overt nephropathy (albuminuria ≥ 300 mg/day).

First Line Therapy:

	RECOMMENDED AGENTS	PAGE LISTING SPECIFIC AGENTS	GRADE OF RECOMMENDATION
	ACE inhibitor	Page 36	A
Special Circumstances:			
<i>If ACE inhibitors are not tolerated USE</i>	angiotensin II antagonist	Page 38	B

NOTE:

Refer to other references for more details on the management of hypertension⁹⁰.

- * In the UKPDS, ACE inhibitors and beta-blockers were not significantly different with respect to blood pressure control and prevention of microalbuminuria and proteinuria. Beta-blocker therapy may be less desirable based on its masking effect of adrenergic symptoms of hypoglycemia.

Section IV: Preventing Complications

Recommendations:

For patients with all of the following conditions:

- diabetes mellitus
- hypertension (BP $\geq$ 140/90 mmHg)
- ABSENCE of overt nephropathy (albuminuria < 300 mg/day)
- age < 60 years.

First Line Therapy:

	RECOMMENDED AGENTS	PAGE LISTING SPECIFIC AGENTS	GRADE OF RECOMMENDATION
Special Circumstances:	ACE inhibitor *	Page 36	A
	OR		
	cardioselective beta-blocker†	Page 37	A
	If ACE inhibitors are not tolerated or contraindicated USE		
	low-dose thiazide‡	Page 37	B
	OR		
	long-acting calcium channel blocker	Page 37	B
	OR		
	angiotensin II antagonist	Page 38	B
	OR		
	α-adrenergic antagonists	Page 38	C

NOTE:

Refer to other references for more details on the management of hypertension⁶⁰.

* ACE inhibitors may be substituted with an angiotensin II receptor antagonist if it is not tolerated⁶⁰.

† In the UKPDS, ACE inhibitors and beta-blockers were not significantly different with respect to blood pressure control and prevention of microalbuminuria and proteinuria. Beta-blocker therapy may be less desirable based on its masking effect of adrenergic symptoms of hypoglycemia.

‡ Some studies have suggested that diuretic therapy in patients with diabetes, normal renal function and hypertension may be associated with increased mortality⁶¹⁻⁶³. Low-dose thiazides may be substituted with indapamide⁶⁰.

Recommendations:

For patients with all of the following conditions:

- diabetes mellitus
- hypertension (BP $\geq$ 140/90 mmHg)
- ABSENCE of overt nephropathy (albuminuria < 300 mg/day)
- age $\geq$ 60 years.

First Line Therapy:

RECOMMENDED AGENTS	PAGE LISTING SPECIFIC AGENTS	GRADE OF RECOMMENDATION
low-dose thiazide*	Page 37	C
OR		
long-acting calcium channel blocker	Page 37	C
OR		
ACE inhibitor	Page 36	C

NOTE:

Refer to other references for more details on the management of hypertension⁶⁰.

- * Some studies have suggested that diuretic therapy in patients with diabetes, normal renal function and hypertension may be associated with increased mortality⁶¹⁻⁶³.
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Section IV: Preventing Complications

Table 13: ACE inhibitors available in Canada for the management of hypertension

<i>Name</i>	<i>Starting Dose*</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
benazepril	10 mg once daily	10-40 mg once daily	0.68-1.56
or			
captopril	6.25 mg (test dose)	6.25-50 mg three times daily	0.32-1.84
or			
cilazapril	2.5-5 mg once daily	2.5-5 mg once daily	0.68-0.79
or			
enalapril	2.5-5 mg once daily	10-40 mg twice daily	0.96-2.32
or			
fosinopril	10 mg once daily	10-40 mg once daily	0.79-1.90
or			
lisinopril	5-10 mg once daily	10-40 mg once daily	0.81-1.94
or			
perindopril	2-4 mg once daily	4-8 mg once daily	0.75-1.50
or			
quinapril	10 mg once daily	10-40 mg once daily	0.82
or			
ramipril	1.25-2.5 mg once daily	2.5-10 mg once daily	0.75-0.95
or			
trandolapril	0.5-1 mg once daily	1-2 mg once daily	0.67-0.77

NOTE:

- * Patients on concomitant diuretic therapy should, if possible, discontinue the diuretic 2-3 days before starting the ACE inhibitor to minimize hypotension. Otherwise the lowest possible starting dose should be taken under close medical supervision.

Section IV: Preventing Complications

Table 14: Cardioselective beta-adrenergic antagonists available in Canada

<i>Name</i>	<i>Starting Dose</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
acebutolol	100 mg twice daily	100-400 mg twice daily	0.33-0.97
or			
atenolol	50 mg once daily	50-200 mg once daily	0.35-1.16
or			
metoprolol	50 mg twice daily	50-100 mg twice daily	0.25-0.44

Table 15: Long-acting calcium-channel blockers available in Canada

<i>Name</i>	<i>Starting Dose</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
amlodipine	2.5-5 mg once daily	5-10 mg once daily	1.28-1.90
or			
diltiazem	60 mg twice daily	60 twice daily to 360 mg once daily	0.73-2.15
or			
felodipine	2.5-5 mg once daily	5-10 mg once daily	0.66-0.99
or			
nifedipine	20-30 mg once daily	30-90 mg once daily	0.93-2.39
or			
verapamil	120 mg once daily	120-240 mg once daily	0.78-0.87

Table 16: Thiazide-like diuretics available in Canada

<i>Name</i>	<i>Starting Dose</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
chlorthalidone	25 mg once daily	25-50 mg once daily	0.01-0.02
or			
hydrochlorothiazide	12.5 mg once daily	25-50 mg once daily	0.01
or			
indapamide	1.25 mg once daily	1.25-2.5 mg once daily	0.19-0.30

Section IV: Preventing Complications

Table 13: ACE inhibitors available in Canada for the management of hypertension

<i>Name</i>	<i>Starting Dose*</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
benazepril	10 mg once daily	10-40 mg once daily	0.68-1.56
or			
captopril	6.25 mg (test dose)	6.25-50 mg three times daily	0.32-1.84
or			
cilazapril	2.5-5 mg once daily	2.5-5 mg once daily	0.68-0.79
or			
enalapril	2.5-5 mg once daily	10-40 mg twice daily	0.96-2.32
or			
fosinopril	10 mg once daily	10-40 mg once daily	0.79-1.90
or			
lisinopril	5-10 mg once daily	10-40 mg once daily	0.81-1.94
or			
perindopril	2-4 mg once daily	4-8 mg once daily	0.75-1.50
or			
quinapril	10 mg once daily	10-40 mg once daily	0.82
or			
ramipril	1.25-2.5 mg once daily	2.5-10 mg once daily	0.75-0.95
or			
trandolapril	0.5-1 mg once daily	1-2 mg once daily	0.67-0.77

NOTE:

- * Patients on concomitant diuretic therapy should, if possible, discontinue the diuretic 2-3 days before starting the ACE inhibitor to minimize hypotension. Otherwise the lowest possible starting dose should be taken under close medical supervision.

Section IV: Preventing Complications

Table 14: Cardioselective beta-adrenergic antagonists available in Canada

<i>Name</i>	<i>Starting Dose</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
acebutolol	100 mg twice daily	100-400 mg twice daily	0.33-0.97
or			
atenolol	50 mg once daily	50-200 mg once daily	0.35-1.16
or			
metoprolol	50 mg twice daily	50-100 mg twice daily	0.25-0.44

Table 15: Long-acting calcium-channel blockers available in Canada

<i>Name</i>	<i>Starting Dose</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
amlodipine	2.5-5 mg once daily	5-10 mg once daily	1.28-1.90
or			
diltiazem	60 mg twice daily	60 twice daily to 360 mg once daily	0.73-2.15
or			
felodipine	2.5-5 mg once daily	5-10 mg once daily	0.66-0.99
or			
nifedipine	20-30 mg once daily	30-90 mg once daily	0.93-2.39
or			
verapamil	120 mg once daily	120-240 mg once daily	0.78-0.87

Table 16: Thiazide-like diuretics available in Canada

<i>Name</i>	<i>Starting Dose</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
chlorthalidone	25 mg once daily	25-50 mg once daily	0.01-0.02
or			
hydrochlorothiazide	12.5 mg once daily	25-50 mg once daily	0.01
or			
indapamide	1.25 mg once daily	1.25-2.5 mg once daily	0.19-0.30

Section IV: Preventing Complications

Table 17: Angiotensin II receptor antagonists available in Canada

<i>Name</i>	<i>Starting Dose</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
candesartan cilexetil	8 mg once daily	8-16 mg once daily	1.08
or			
irbesartan	75-150 mg once daily	150-300 mg once daily	1.08
or			
losartan	50 mg once daily	50-100 mg once daily	1.10
or			
telmisartan	80 mg once daily	80 mg once daily	1.07
or			
valsartan	80 mg once daily	80-160 mg once daily	1.05

Table 18: Alpha-adrenergic antagonists

<i>Name</i>	<i>Starting Dose</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
doxazosin	1 mg once daily	1-8 mg once daily	0.55-0.72
or			
prazosin	0.5 mg at supper	3-5 mg 2-3 times daily	0.73-1.51
or			
terazosin	1 mg at bedtime	1-5 mg once daily	0.35-0.60

(c) Dyslipidemia**Type 1 and Type 2 Diabetes****Table 19: Treatment goals for managing dyslipidemia in patients with diabetes aged ≥ 30 years^{*, 1,64}**

Risk Factors For CAD	Target Lipid Levels		
	LDL Cholesterol (mmol/L)	Total:HDL Cholesterol Ratio	Triglycerides (mmol/L)
Diabetes and either CAD or a CAD risk factor [†]	< 2.5	< 4.0	< 2.0
Diabetes and no other risk factors	< 3.0	< 5.0	< 3.0

NOTE:

CAD = coronary artery disease, LDL = low density lipoprotein, HDL = high density lipoprotein

* Treatment goals for patients < 30 years of age are uncertain.

† Risk factors for CAD include: family history of premature CAD, smoking and hypertension, LVH (if known)

Recommendations:

- ◆ Diet therapy and physical activity are recommended as the first line approach for patients with dyslipidemia in the absence of CAD.
- ◆ Drug therapy in combination with diet therapy and physical activity is recommended for patients with high lipid levels (LDL ≥ 3.0 mmol/L) in the presence of atherosclerotic disease or when nonpharmacologic measures fail to lower lipid levels adequately following a 3 month trial^{64,65}.

Grade of recommendations – A**Recommendations:**

- ◆ HMG CoA reductase inhibitors are the agents of choice in the presence of elevated LDL^{66,67}.
- ◆ Bile acid binding resins⁶⁸ or fibric acid derivatives⁶⁹ are recommended as second line agents in the presence of elevated LDL.
- ◆ For hypertriglyceridemia (in the presence of normal LDL levels), fibric acid derivatives are recommended as first line therapy⁷⁰.

Grade of recommendations – B**NOTE:**

Niacin is relatively contraindicated in diabetes mellitus due to its hyperglycemic effects (especially at high doses).

Section IV: Preventing Complications

Table 17: Angiotensin II receptor antagonists available in Canada

<i>Name</i>	<i>Starting Dose</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
candesartan cilexetil	8 mg once daily	8-16 mg once daily	1.08
or			
irbesartan	75-150 mg once daily	150-300 mg once daily	1.08
or			
losartan	50 mg once daily	50-100 mg once daily	1.10
or			
telmisartan	80 mg once daily	80 mg once daily	1.07
or			
valsartan	80 mg once daily	80-160 mg once daily	1.05

Table 18: Alpha-adrenergic antagonists

<i>Name</i>	<i>Starting Dose</i>	<i>Usual Maintenance Dose</i>	<i>Daily Cost (\$)</i>
doxazosin	1 mg once daily	1-8 mg once daily	0.55-0.72
or			
prazosin	0.5 mg at supper	3-5 mg 2-3 times daily	0.73-1.51
or			
terazosin	1 mg at bedtime	1-5 mg once daily	0.35-0.60

(c) Dyslipidemia**Type 1 and Type 2 Diabetes****Table 19: Treatment goals for managing dyslipidemia in patients with diabetes aged ≥ 30 years* ^{1,64}**

Risk Factors For CAD	Target Lipid Levels		
	LDL Cholesterol (mmol/L)	Total:HDL Cholesterol Ratio	Triglycerides (mmol/L)
Diabetes and either CAD or a CAD risk factor [†]	< 2.5	< 4.0	< 2.0
Diabetes and no other risk factors	< 3.0	< 5.0	< 3.0

NOTE:

CAD = coronary artery disease, LDL = low density lipoprotein, HDL = high density lipoprotein

* Treatment goals for patients < 30 years of age are uncertain.

† Risk factors for CAD include: family history of premature CAD, smoking and hypertension, LVH (if known)

Recommendations:

- ◆ Diet therapy and physical activity are recommended as the first line approach for patients with dyslipidemia in the absence of CAD.
- ◆ Drug therapy in combination with diet therapy and physical activity is recommended for patients with high lipid levels (LDL ≥ 3.0 mmol/L) in the presence of atherosclerotic disease or when nonpharmacologic measures fail to lower lipid levels adequately following a 3 month trial^{164,65}.

Grade of recommendations – A**Recommendations:**

- ◆ HMG CoA reductase inhibitors are the agents of choice in the presence of elevated LDL^{66,67}.
- ◆ Bile acid binding resins⁶⁸ or fibric acid derivatives⁶⁹ are recommended as second line agents in the presence of elevated LDL.
- ◆ For hypertriglyceridemia (in the presence of normal LDL levels), fibric acid derivatives are recommended as first line therapy⁷⁰.

Grade of recommendations – B**NOTE:**

Niacin is relatively contraindicated in diabetes mellitus due to its hyperglycemic effects (especially at high doses).

Section IV: Preventing Complications

Table 19: HMG-CoA reductase inhibitors available in Canada

<i>Name</i>	<i>Recommended Daily Dose</i>	<i>Daily Cost (\$)</i>
atorvastatin	10-80 mg once daily	1.60-4.30
or		
cerivastatin	0.2-0.4 mg once daily	1.20-1.60
or		
fluvastatin	20 mg once daily – 40 mg twice daily	0.75-2.10
or		
lovastatin	20-80 mg with supper	1.30-4.79
or		
pravastatin	10-40 mg in the evening	1.51-2.15
or		
simvastatin	5-80 mg in the evening	0.90-2.20

Table 20: Fibric acid derivatives available in Canada

<i>Name</i>	<i>Recommended Daily Dose</i>	<i>Daily Cost (\$)</i>
bezafibrate	400 mg once daily	1.60
or		
fenofibrate	200 mg once daily	1.73
or		
gemfibrozil	600 mg twice daily	1.39

NOTE: Take with evening meal

Table 21: Bile-acid binding resins available in Canada

<i>Name</i>	<i>Recommended Daily Dose</i>	<i>Daily Cost (\$)</i>
cholestyramine	4-24 g daily	0.47-2.85
or		
colestipol	5-30 g daily	0.77-4.60

NOTE: Divide into 3-5 portions

(d) Coronary Artery Disease**Type 1 and Type 2 Diabetes****Recommendations:**

- ◆ Low-dose ASA is recommended as secondary prevention for all patients (age ≥ 30 years) with type 2 diabetes with coronary artery disease (eg. previous myocardial infarction, angina, stroke) and as primary prevention in patients with type 2 diabetes at high risk* of cardiovascular disease^{71,72}.
- ◆ Add an ACE inhibitor in patients age > 55 years old with any one of the following: a previous cardiac event, dyslipidemia (HDL < 0.9 mmol/L or total cholesterol > 5.2 mmol/L), microalbuminuria or hypertension⁷³.

Grade of recommendations – A**NOTE:**

These recommendations do not apply to patients < 30 years old

All modifiable risk factors for CAD should be treated including hyperlipidemia, hypertension, and smoking.

* Risk factors for CAD include: family history of premature CAD, smoking, hypertension, and low HDL (≤ 0.9 mmol/L).

Table 22: Antiplatelet therapy available in Canada for prevention of coronary artery disease complications

<i>Name</i>	<i>Daily Dosage</i>	<i>Daily Cost (\$)</i>
enteric coated ASA	81 or 325 mg once daily	0.13 or 0.02

Section IV: Preventing Complications

Table 19: HMG-CoA reductase inhibitors available in Canada

<i>Name</i>	<i>Recommended Daily Dose</i>	<i>Daily Cost (\$)</i>
atorvastatin	10-80 mg once daily	1.60-4.30
or		
cerivastatin	0.2-0.4 mg once daily	1.20-1.60
or		
fluvastatin	20 mg once daily – 40 mg twice daily	0.75-2.10
or		
lovastatin	20-80 mg with supper	1.30-4.79
or		
pravastatin	10-40 mg in the evening	1.51-2.15
or		
simvastatin	5-80 mg in the evening	0.90-2.20

Table 20: Fibric acid derivatives available in Canada

<i>Name</i>	<i>Recommended Daily Dose</i>	<i>Daily Cost (\$)</i>
bezafibrate	400 mg once daily	1.60
or		
fenofibrate	200 mg once daily	1.73
or		
gemfibrozil	600 mg twice daily	1.39

NOTE: Take with evening meal

Table 21: Bile-acid binding resins available in Canada

<i>Name</i>	<i>Recommended Daily Dose</i>	<i>Daily Cost (\$)</i>
cholestyramine	4-24 g daily	0.47-2.85
or		
colestipol	5-30 g daily	0.77-4.60

NOTE: Divide into 3-5 portions

(d) Coronary Artery Disease**Type 1 and Type 2 Diabetes****Recommendations:**

- ◆ Low-dose ASA is recommended as secondary prevention for all patients (age ≥ 30 years) with type 2 diabetes with coronary artery disease (eg. previous myocardial infarction, angina, stroke) and as primary prevention in patients with type 2 diabetes at high risk* of cardiovascular disease^{71,72}.
- ◆ Add an ACE inhibitor in patients age > 55 years old with any one of the following: a previous cardiac event, dyslipidemia (HDL < 0.9 mmol/L or total cholesterol > 5.2 mmol/L), microalbuminuria or hypertension⁷³.

Grade of recommendations – A**NOTE:**

These recommendations do not apply to patients < 30 years old

All modifiable risk factors for CAD should be treated including hyperlipidemia, hypertension, and smoking.

* Risk factors for CAD include: family history of premature CAD, smoking, hypertension, and low HDL (≤ 0.9 mmol/L).

Table 22: Antiplatelet therapy available in Canada for prevention of coronary artery disease complications

<i>Name</i>	<i>Daily Dosage</i>	<i>Daily Cost (\$)</i>
enteric coated ASA	81 or 325 mg once daily	0.13 or 0.02

Section IV: Preventing Complications

Table 23: ACE inhibitors available in Canada for the primary and secondary prevention of coronary artery disease events			
Name	Starting Dose*	Optimal Dose	Daily Cost (\$)
Agents with published randomized controlled trials supporting this indication			
ramipril	1.25-2.5 mg once daily	10 mg once daily	0.95
Agents without published randomized controlled trials supporting this indication			
benazepril	10 mg once daily	10-40 mg once daily	0.68-1.56
or			
captopril	6.25 mg (test dose)	6.25-50 mg 3 times daily	0.32-1.68
or			
cilazapril	2.5-5 mg once daily	2.5-5 mg once daily	0.68-0.79
or			
enalapril	2.5-5 mg once daily	10-40 mg once daily	0.96-2.32
or			
fosinopril	10 mg once daily	10-20 mg once daily	0.79-0.95
or			
lisinopril	2.5-10 mg once daily	10-40 mg once daily	0.81-1.94
or			
perindopril	2-4 mg once daily	4-8 mg once daily	0.75-1.50
or			
quinapril	10 mg once daily	10-40 mg once daily	0.82
or			
trandolapril	0.5-1 mg once daily	0.5-4 mg once daily	0.34-1.54

NOTE:

For the complete therapeutic management of ischemic heart disease, physicians should refer to the OPOT guidelines titled 'Ontario Drug Therapy Guidelines for Stable Ischemic Heart Disease in Primary Care'.

- * Patients on concomitant diuretic therapy should, if possible, discontinue the diuretic 2-3 days before starting the ACE inhibitor to minimize hypotension. Otherwise the lowest possible starting dose should be taken under close medical supervision.

Section IV: Preventing Complications

Table 23: ACE inhibitors available in Canada for the primary and secondary prevention of coronary artery disease events

<i>Name</i>	<i>Starting Dose*</i>	<i>Optimal Dose</i>	<i>Daily Cost (\$)</i>
Agents with published randomized controlled trials supporting this indication			
ramipril	1.25-2.5 mg once daily	10 mg once daily	0.95
Agents without published randomized controlled trials supporting this indication			
benazepril	10 mg once daily	10-40 mg once daily	0.68-1.56
or			
captopril	6.25 mg (test dose)	6.25-50 mg 3 times daily	0.32-1.68
or			
cilazapril	2.5-5 mg once daily	2.5-5 mg once daily	0.68-0.79
or			
enalapril	2.5-5 mg once daily	10-40 mg once daily	0.96-2.32
or			
fosinopril	10 mg once daily	10-20 mg once daily	0.79-0.95
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quinapril	10 mg once daily	10-40 mg once daily	0.82
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trandolapril	0.5-1 mg once daily	0.5-4 mg once daily	0.34-1.54

NOTE:

For the complete therapeutic management of ischemic heart disease, physicians should refer to the OPOT guidelines titled 'Ontario Drug Therapy Guidelines for Stable Ischemic Heart Disease in Primary Care'.

* Patients on concomitant diuretic therapy should, if possible, discontinue the diuretic 2-3 days before starting the ACE inhibitor to minimize hypotension. Otherwise the lowest possible starting dose should be taken under close medical supervision.

Section V

Gestational Diabetes Mellitus

Ontario Program for Optimal Therapeutics

**IMPORTANT NOTE CONCERNING THE FOLLOWING
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Section V: Gestational Diabetes Mellitus

Defined as diabetes mellitus with onset or first recognition during pregnancy².

Recommendations:

- ◆ Diet therapy, moderate exercise and education is recommended as the first line approach to glycemic control^{1,74,75}.
- ◆ Insulin is added as needed to achieve glycemic control where fasting blood glucose is > 5.3 mmol/L and 2 hour postprandial glucose is > 8.9 mmol/L^{1,76}.
- ◆ Lispro can be used during pregnancy as there is sufficient safety data^{77,78}.
- ◆ Oral hypoglycemics should not be used during pregnancy due to potential harm to the fetus⁷⁹.

Grade of recommendations – C

NOTE:

Patients with type 1 diabetes who are pregnant require shared care with a primary care physician and a specialist.

Section V: Gestational Diabetes Mellitus

Defined as diabetes mellitus with onset or first recognition during pregnancy².

Recommendations:

- ◆ Diet therapy, moderate exercise and education is recommended as the first line approach to glycemic control^{1,74,75}.
- ◆ Insulin is added as needed to achieve glycemic control where fasting blood glucose is > 5.3 mmol/L and 2 hour postprandial glucose is > 8.9 mmol/L^{1,76}.
- ◆ Lispro can be used during pregnancy as there is sufficient safety data^{77,78}.
- ◆ Oral hypoglycemics should not be used during pregnancy due to potential harm to the fetus⁷⁹.

Grade of recommendations – C

NOTE:

Patients with type 1 diabetes who are pregnant require shared care with a primary care physician and a specialist.

Reference List

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Appendices

Ontario Program for Optimal Therapeutics



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Appendices

Appendices

Table 24: Diagnostic criteria for Diabetes Mellitus¹

- (a) A casual (random) plasma glucose value ≥ 11.1 mmol/L accompanied by symptoms* of diabetes
OR
- (b) A fasting plasma glucose (FPG) ≥ 7.0 mmol/L[†]
OR
- (c) A plasma glucose value in the 2-h sample (2hPG) of the oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L

NOTE:

The diagnosis is based on venous plasma glucose concentrations using the criteria listed above. In the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation, a confirmatory test must be performed on another day in all cases.

According to the Canadian guidelines, HbA_{1c} is unsuitable for diagnostic purposes as this test has not been standardized².

* The classic symptoms of diabetes include:

- fatigue
- polyuria
- polydipsia, and
- unexplained weight loss.

† Fasting plasma glucose is defined as no caloric intake for at least 8 hours.

Table 25: Glucose Levels for the Diagnostic Categories¹

Category	FPG (mmol/L)	PG 1h after 75 g glucose load (mmol/L)	PG 2 h after 75 g glucose load (mmol/L)
Impaired fasting glucose (IFG)	6.1 – 6.9	N/A	N/A
Impaired glucose tolerance (IGT)	< 7.0	N/A	7.8 – 11.0
Diabetes mellitus	≥ 7.0	N/A	≥ 11.1
Gestational diabetes mellitus*	≥ 5.3	≥ 10.6	≥ 8.9

NOTE:

FPG = fasting plasma glucose; PG = plasma glucose; N/A = not applicable

* A diagnosis of gestational diabetes mellitus requires 2 abnormal values among the 3 measurements.

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NOTE:

FPG = fasting plasma glucose; PG = plasma glucose; N/A = not applicable

* A diagnosis of gestational diabetes mellitus requires 2 abnormal values among the 3 measurements.

Examples of possible methods for initiating insulin therapy in a patient with type 1 diabetes:*

Intensive Insulin Regimen (optimal glycemic control):

Estimate total daily dose: 0.3-0.6 units / kg

Divide total daily dose: 40-50% of daily basal dose
50-60% of total daily pre-meal doses

Administer basal dose(s) as: a single dose of intermediate-acting insulin[†] qHS
OR
a divided dose of long-acting insulin[†] twice daily

Divide total daily pre-meal doses (the following split assumes a 'normal' mealtime distribution of calories):

5/12 (42%) = breakfast
3/12 (25%) = lunch
4/12 (33%) = supper

Administer pre-meal doses as a short-acting insulin/insulin analogue

Initially, insulin should be adjusted approximately every 3 days based on blood glucose concentrations (taken at least 4 times daily)

Split-mixed Regimen (appropriate when optimal glycemic control is contraindicated and less than optimal glycemic control is the treatment goal):

Estimate total daily dose: 0.3-0.6 units / kg

Divide total daily dose: 2/3 = morning dose (before breakfast)
1/3 = evening dose (before supper)

Divide each dose:

If age ≥ 5 years: 2/3 intermediate-acting insulin[†]
1/3 short-acting insulin/insulin analogue

If age < 5 years: 3/4 intermediate-acting insulin[†]
1/4 short-acting insulin/insulin analogue

Initially, insulin should be adjusted approximately every 3 days based on blood glucose concentrations (taken 4 times daily)

Grade of recommendations – C

NOTE:

- * The methods for starting insulin presented here are examples based solely on clinical experience. There is no evidence to suggest that these are the most effective methods of initiating insulin.
- † Insulin zinc (lente or ultralente) must not be mixed and left to stand (> 5 minutes) with regular insulin as excess zinc in insulin zinc will bind with regular insulin and slow its onset of action.

Two examples of possible methods for initiating insulin therapy in a patient with type 2 diabetes:

Adding Insulin to oral hypoglycemic agents:

Add a bedtime dose of insulin

intermediate-acting insulin: 10-15 units (maximum 0.25 units/kg)

Increase insulin dose by 2 units every 3-4 days until fasting glucose is 4-7 mmol/L.

If target blood glucose concentrations not achieved at 30 units / day or if daytime blood glucose concentrations rise during the day, switch to a split-mixed insulin or more intensive regimen.

Split-mixed Regimen:

Discontinue oral hypoglycemic agents

Estimate total starting daily dose: 0.3-0.6 units / kg

Divide total daily dose: $\frac{2}{3}$ = morning dose (before breakfast)
 $\frac{1}{3}$ = evening dose (before supper)

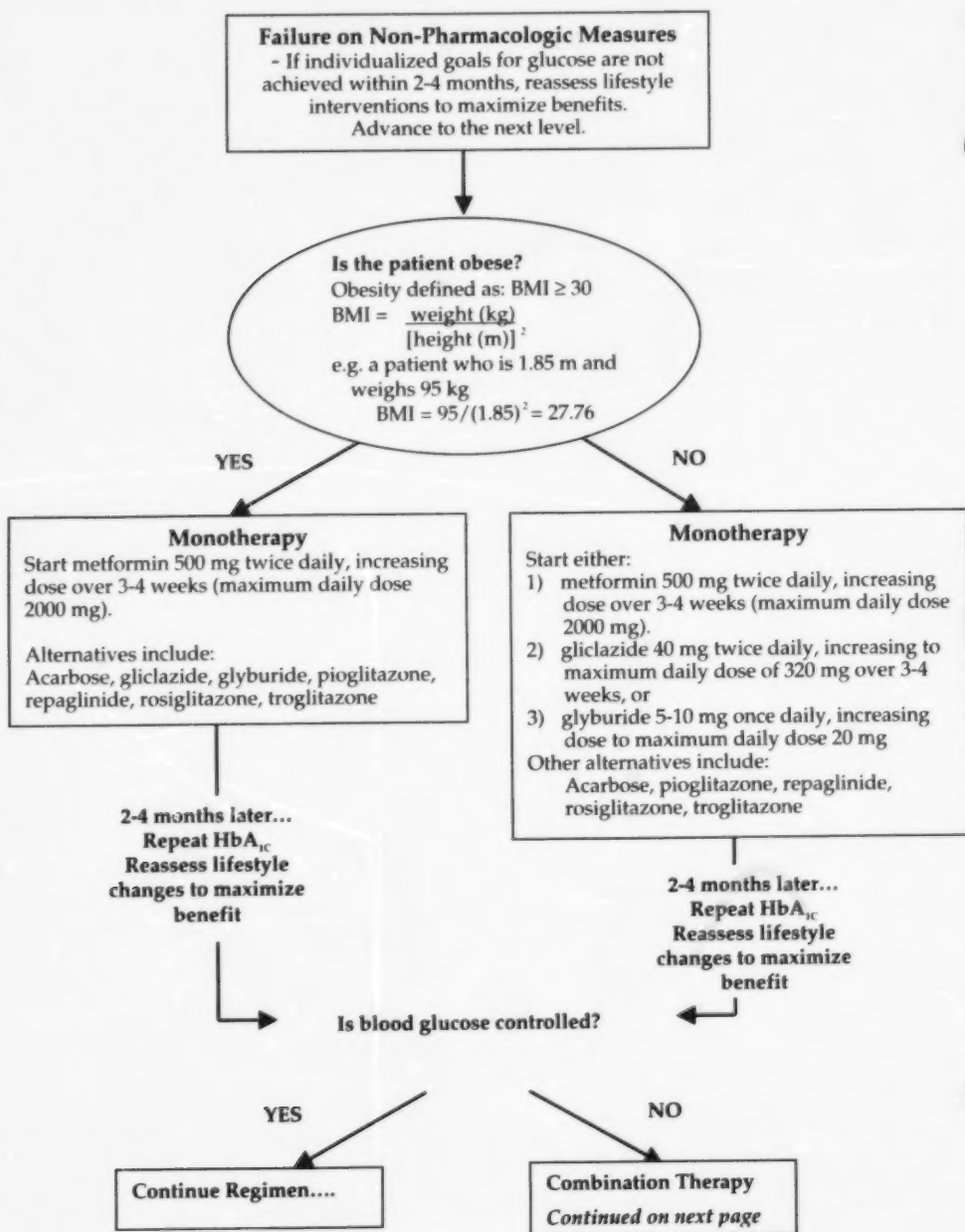
Divide each dose: $\frac{2}{3}$ intermediate-acting insulin
 $\frac{1}{3}$ short-acting insulin/insulin analogue

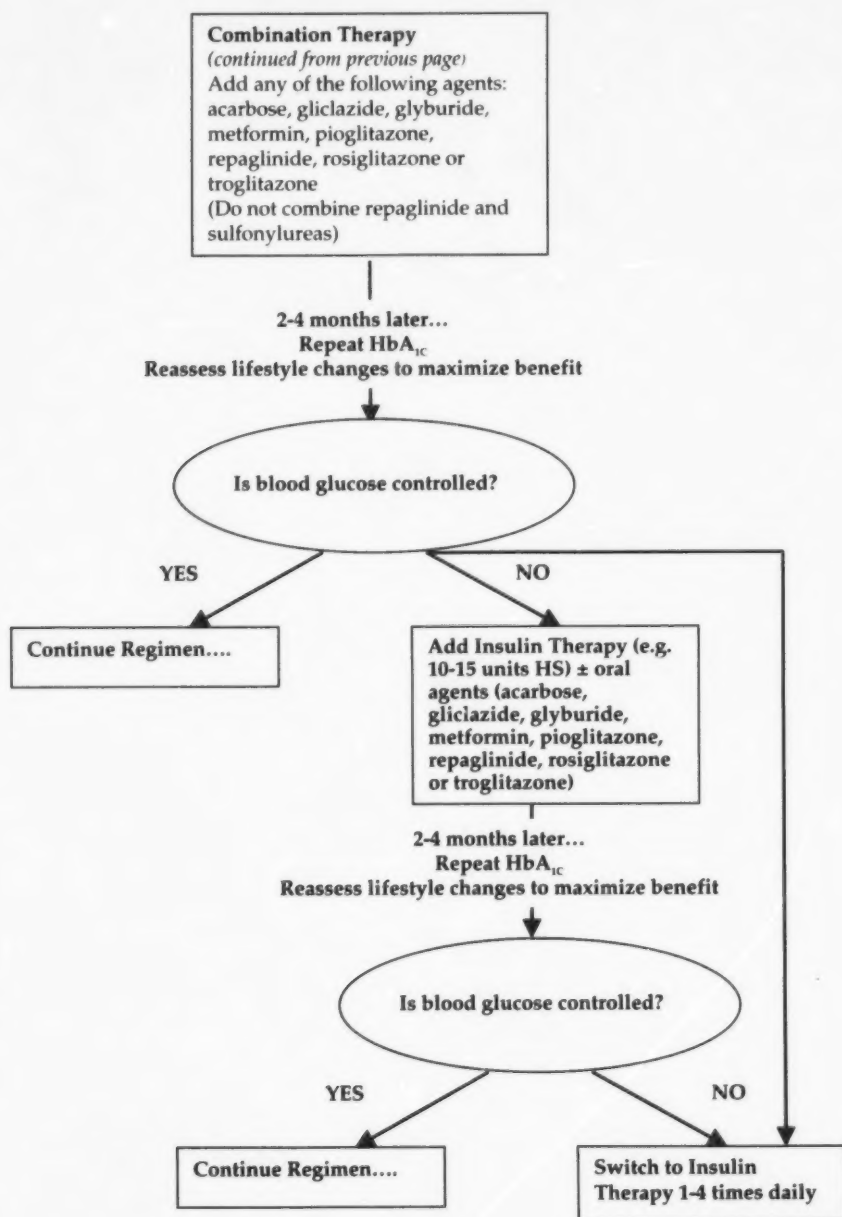
Grade of recommendations – C

NOTE:

Insulin zinc (lente or ultralente) must not be mixed with regular insulin and left to stand (> 5 minutes) as excess zinc in insulin zinc will bind with regular insulin and slow its onset of action.

Figure 3: Detailed algorithm for the drug management of type 2 diabetes





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Body Mass Index (kg/m²) Nomogram

Height (Meters)	Weight (Kg)																	
	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130
1.50	20.0	22.2	24.4	26.7	28.9	31.1	33.3	35.6	37.8	40.0	42.2	44.4	46.7	48.9	51.1	53.3	55.6	57.8
1.55	18.7	20.8	22.9	25.0	27.1	29.1	31.2	33.3	35.4	37.5	39.5	41.6	43.7	45.8	47.9	49.9	52.0	54.1
1.60	17.6	19.5	21.5	23.4	25.4	27.3	29.3	31.3	33.2	35.2	37.1	39.1	41.0	43.0	44.9	46.9	48.8	50.8
1.65	16.5	18.4	20.2	22.0	23.9	25.7	27.5	29.4	31.2	33.1	34.9	36.7	38.6	40.4	42.2	44.1	45.9	47.8
1.70	15.6	17.3	19.0	20.8	22.5	24.2	26.0	27.7	29.4	31.1	32.9	34.6	36.3	38.1	39.8	41.5	43.3	45.0
1.75	14.7	16.3	18.0	19.6	21.2	22.9	24.5	26.1	27.8	29.4	31.0	32.7	34.3	35.9	37.6	39.2	40.8	42.4
1.80	13.9	15.4	17.0	18.5	20.1	21.6	23.1	24.7	26.2	27.8	29.3	30.9	32.4	34.0	35.5	37.0	38.6	40.1
1.85	13.1	14.6	16.1	17.5	19.0	20.5	21.9	23.4	24.8	26.3	27.8	29.2	30.7	32.1	33.6	35.1	36.5	38.0
1.90	12.5	13.9	15.2	16.6	18.0	19.4	20.8	22.2	23.5	24.9	26.3	27.7	29.1	30.5	31.9	33.2	34.6	36.0
1.95	11.8	13.1	14.5	15.8	17.1	18.4	19.7	21.0	22.4	23.7	25.0	26.3	27.6	28.9	30.2	31.6	32.9	34.2
2.00	11.3	12.5	13.8	15.0	16.3	17.5	18.8	20.0	21.3	22.5	23.8	25.0	26.3	27.5	28.8	30.0	31.3	32.5
2.05	10.7	11.9	13.1	14.3	15.5	16.7	17.8	19.0	20.2	21.4	22.6	23.8	25.0	26.2	27.4	28.6	29.7	30.9
2.10	10.2	11.3	12.5	13.6	14.7	15.9	17.0	18.1	19.3	20.4	21.5	22.7	23.8	24.9	26.1	27.2	28.3	29.5
2.15	9.7	10.8	11.9	13.0	14.1	15.1	16.2	17.3	18.4	19.5	20.6	21.6	22.7	23.8	24.9	26.0	27.0	28.1
2.20	9.3	10.3	11.4	12.4	13.4	14.5	15.5	16.5	17.6	18.6	19.6	20.7	21.7	22.7	23.8	24.8	25.8	26.9
2.25	8.9	9.9	10.9	11.9	12.8	13.8	14.8	15.8	16.8	17.8	18.8	19.8	20.7	21.7	22.7	23.7	24.7	25.7
2.30	8.5	9.5	10.4	11.3	12.3	13.2	14.2	15.1	16.1	17.0	18.0	18.9	19.8	20.8	21.7	22.7	23.6	24.6

NOTE:²¹

Underweight: < 18.5 kg/m²
 Normal: 18.5-24.9 kg/m² (shaded area)
 Overweight: 25.0-29.9 kg/m²
 Obese: ≥ 30.0 kg/m²

Body Mass Index (kg/m²) Nomogram

Height (Meters)	Weight (Kg)										110	115	120	125	130			
	45	50	55	60	65	70	75	80	85	90						95	100	105
1.50	20.0	22.2	24.4	26.7	28.9	31.1	33.3	35.6	37.8	40.0	42.2	44.4	46.7	48.9	51.1	53.3	55.6	57.8
1.55	18.7	20.8	22.9	25.0	27.1	29.1	31.2	33.3	35.4	37.5	39.5	41.6	43.7	45.8	47.9	49.9	52.0	54.1
1.60	17.6	19.5	21.5	23.4	25.4	27.3	29.3	31.3	33.2	35.2	37.1	39.1	41.0	43.0	44.9	46.9	48.8	50.8
1.65	16.5	18.4	20.2	22.0	23.9	25.7	27.5	29.4	31.2	33.1	34.9	36.7	38.6	40.4	42.2	44.1	45.9	47.8
1.70	15.6	17.3	19.0	20.8	22.5	24.2	26.0	27.7	29.4	31.1	32.9	34.6	36.3	38.1	39.8	41.5	43.3	45.0
1.75	14.7	16.3	18.0	19.6	21.2	22.9	24.5	26.1	27.8	29.4	31.0	32.7	34.3	35.9	37.6	39.2	40.8	42.4
1.80	13.9	15.4	17.0	18.5	20.1	21.6	23.1	24.7	26.2	27.8	29.3	30.9	32.4	34.0	35.5	37.0	38.6	40.1
1.85	13.1	14.6	16.1	17.5	19.0	20.5	21.9	23.4	24.8	26.3	27.8	29.2	30.7	32.1	33.6	35.1	36.5	38.0
1.90	12.5	13.9	15.2	16.6	18.0	19.4	20.8	22.2	23.5	24.9	26.3	27.7	29.1	30.5	31.9	33.2	34.6	36.0
1.95	11.8	13.1	14.5	15.8	17.1	18.4	19.7	21.0	22.4	23.7	25.0	26.3	27.6	28.9	30.2	31.6	32.9	34.2
2.00	11.3	12.5	13.8	15.0	16.3	17.5	18.8	20.0	21.3	22.5	23.8	25.0	26.3	27.5	28.8	30.0	31.3	32.5
2.05	10.7	11.9	13.1	14.3	15.5	16.7	17.8	19.0	20.2	21.4	22.6	23.8	25.0	26.2	27.4	28.6	29.7	30.9
2.10	10.2	11.3	12.5	13.6	14.7	15.9	17.0	18.1	19.3	20.4	21.5	22.7	23.8	24.9	26.1	27.2	28.3	29.5
2.15	9.7	10.8	11.9	13.0	14.1	15.1	16.2	17.3	18.4	19.5	20.6	21.6	22.7	23.8	24.9	26.0	27.0	28.1
2.20	9.3	10.3	11.4	12.4	13.4	14.5	15.5	16.5	17.6	18.6	19.6	20.7	21.7	22.7	23.8	24.8	25.8	26.9
2.25	8.9	9.9	10.9	11.9	12.8	13.8	14.8	15.8	16.8	17.8	18.8	19.8	20.7	21.7	22.7	23.7	24.7	25.7
2.30	8.5	9.5	10.4	11.3	12.3	13.2	14.2	15.1	16.1	17.0	18.0	18.9	19.8	20.8	21.7	22.7	23.6	24.6

NOTE:^a

Underweight:

< 18.5 kg/m²

Normal:

18.5-24.9 kg/m² (shaded area)

Overweight:

25.0-29.9 kg/m²

Obese:

≥ 30.0 kg/m²

Summary of Landmark Studies

Diabetes Control and Complications Trial (DCCT)⁸

Limitations

- (a) Limited to 1441 patients with type 1 diabetes without advanced complications

Intervention

- (a) Intensive insulin therapy versus conventional glycemic control

Findings

- (a) Intensive insulin therapy delayed the onset and progression of microvascular complications.
- (b) There was a 3-fold greater risk of hypoglycemia with intensive glycemic control compared to conventional treatment.
- (c) Intensive insulin therapy was achieved using either: multiple daily injections (3 or more) or treatment with an insulin pump.
- (d) Any improvement in glycemic control has been shown to delay the onset and progression of microvascular complications.
- (e) The mean HbA_{1c} in the intensive group was 7.2% (versus 9% in conventional treatment group).
- (f) The intensive group experienced significantly more weight gain (mean 4.6 g).
- (g) Reductions in cardiovascular events were not statistically significant.

United Kingdom Prospective Diabetes Study (UKPDS)^{22,26,52}

Limitations

- (a) Limited to 3867 newly diagnosed subjects with type 2 diabetes.

Intervention

- (a) Intensive glycemic control versus conventional dietary measures.
- (b) A sub-study of 1704 overweight subjects allocated to diet versus metformin therapy
- (c) A sub-study of 1148 subjects with hypertension were randomized to intensive versus less intensive blood pressure control. Those assigned to intensive blood pressure control were randomized to receive either captopril or atenolol.

Findings

Intensive glycemic control versus conventional dietary measures

- (a) Overall microvascular complication rate decreased by 25% with intensive glycemic control.
- (b) Improved glycemic control reduces retinopathy, nephropathy and possibly neuropathy.
- (c) HbA_{1c} difference of 7.0% versus 7.9%.
- (d) No significant impact on cardiovascular complications (16% relative risk reduction in combined fatal or non-fatal myocardial infarction and sudden death did not achieve statistical significance $p=0.052$).
- (e) Epidemiological analysis showed that there is no glycemic threshold (i.e. any improvement in glycemic control will result in some reduction of microvascular complications).
- (f) Highest incidence of hypoglycemic events was 2.3% in insulin treated patients.
- (g) There was a marginally significant decrease in cardiovascular events in both sulfonylurea or insulin treated patients.

Metformin sub-study

- (h) Metformin resulted in a statistically significant combined decrease risk of diabetes-related end points, diabetes-related deaths, all-cause deaths, and myocardial infarction by approximately 1/3 as compared to conventional dietary measures.
- (i) In patients where metformin was added to a sulfonylurea, there was a 96% relative increase in diabetes-related death ($p < 0.04$). The clinical importance of this result is not yet clear.

Intensive blood pressure control versus conventional blood pressure control sub-study

- (j) Intensive blood pressure control (mean blood pressure of 144/82 mm hg) versus less intensive blood pressure control (mean blood pressure of 154/87) resulted in significant relative risk reductions in most microvascular and cardiovascular outcomes (24-56%). Reductions in myocardial infarctions were not significant.
- (k) Ace inhibitors and beta-blockers were equally effective at lowering blood pressure and cardiovascular events. There was no significant difference in microalbuminuria or proteinurea.